UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Review of Revised Acute Toxicity Waiver Guidance Document

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The attached document was generated in response to the 1992 Reregistration Workshop in order to give guidance to registrants seeking waivers for acute toxicity studies. It outlines certain study-specific criteria which are usually considered upon review of an acute waiver request. This document was previously reviewed by Beth Doyle (Tox Branch II) and John Redden (Tox Branch I), however, additional revisions have since been performed. We are requesting that Toxicology Branch II review and provide comment on the revised document. Toxicology Branch I has also been sent a revised copy for review.

If you have any questions please contact Mark Perry at 308-8335. We would appreciate all comments by July 30.

ACUTE TOXICITY WAIVER GUIDANCE DOCUMENT

This document was produced in response to the 1992 Reregistration Workshop. Its purpose is to assist registrants in determining if a request for an acute toxicity waiver is appropriate and likely to be found acceptable. The following guidance should ultimately save time and resources not only for the registrant, but for the Agency as well by reducing the number of unacceptable waiver requests submitted. In addition, acceptable waiver requests will also reduce the number of animals tested.

As described in 40CFR §158.45, the primary reasons a data requirement may be waived are that: 1) it is not possible to generate the required data, or 2) the data would not be useful in the Agency's evaluation of the risks or benefits of the product. As an example, a product may have unusual physical, chemical, or biological properties or atypical use patterns making the data requirement inappropriate. In order to waive a data requirement the Agency must have sufficient data available to make the required determination.

Waivers of data requirements are considered on a case-by-case basis in response to specific written requests by registrants. The waiver request must identify the specific data requirement, explain why the applicant thinks it should be waived, describe any unsuccessful attempts to generate the required data, furnish any other information supporting the request, and when appropriate suggest alternative means of obtaining data to address the concern underlying the data requirement. In addition, a discussion of the use pattern and the potential for human exposure should be addressed.

It should be noted that waivers are often granted under the condition that certain precautionary labeling will be required. In these cases, information gathered from other sources will be used to establish the appropriate labeling, hence, the applicant should provide supplemental data. Any acute toxicity information should be submitted which pertains to the acute toxicity data requirement under consideration for a waiver. This may include Material Safety Data Sheets on the individual components and technical bulletins for the product formulation.

Although all waiver requests are addressed on a case-by-case basis, certain general criteria considered upon waiver evaluation can be identified. The following pages outline particular study-specific conditions under which an acute waiver request may be considered. Also included is a brief discussion of specific circumstances which do not justify an acute waiver.

A. ACUTE ORAL TOXICITY

An acute oral toxicity waiver may be requested if either of the following conditions apply:

- The test material is a gas or is highly volatile.

- The test material is a non-friable material and is too large to be ingested or the

product design prevents oral exposure. Products such as pet collars, plastic ear tags and tamper-proof roach traps and bait boxes often meet these criteria. Even though some products may be too large to be ingested, there is some concern when these products are used in and around the home due to children's chewing, licking and sucking behavior. In these cases a waiver may be requested based upon the oral toxicity of the individual components of the pesticide product and the quantity of each component contained in one of the large units.

B. ACUTE DERMAL TOXICITY

An acute dermal toxicity waiver may be requested if any of the following conditions apply:

- The test material is corrosive to skin or has a pH less than 2 or greater than 11.5. These products will be placed in dermal toxicity category I on the basis of potential dermal effects.

- The product design prevents dermal exposure. Products such as tamper-proof roach traps and bait boxes often meet these criteria.

- The test material has been placed in category I for primary dermal irritation. These products will be placed in dermal toxicity category I on the basis of potential dermal effects.

C. ACUTE INHALATION TOXICITY

According to 40CFR an acute inhalation study is required if the test material consists of, or under conditions of use will result in, an inhalable material (e.g., gas, volatile substances, or aerosol/particulate). Since this statement is rather general, the following provides more specific guidance to assist in determining if a waiver request is appropriate. If any of the following conditions apply, an acute inhalation toxicity waiver may be requested:

- The test material is a gum, wax or resin that is non-friable, does not form aerosols and has a low vapor pressure. The performance of an attrition study may be required to demonstrate that the test material is non-friable. Alternatively a hands-on inspection of the material by the reviewer may suffice.

- The test material is a plastic material that is large in size, non-friable and does not possess any volatile hazardous components. Pet collars and plastic ear tags often meet these criteria.

• The product design prevents inhalation exposure during all phases of product use.

• The test material is microencapsulated and conforms to all of the following criteria [obtained from the 3/8/91 Agency memo from John Whalen (HED) to George LaRocca (PM-13)]:

-The capsular material is toxicologically inert and capsules do not tend to fracture or leak.

-There are a wide range of optical diameters. Most particles are not inhalable and none are respirable (< 4μm MMAD).

-Particles entering the nose would be captured in the nasal area. Capsules would remain intact and pose no risk of absorption through the nasal mucosa.

-Particles captured in the nasal mucus would either be expelled or swallowed, thus would not result in any toxicity via respiration.

-The product cannot be generated in an inhalation chamber as a dust because of its sticky nature, or as a liquid aerosol because the capsules are too large for nebulization. The only method of generation of the pesticide product as an aerosol is by use with a spray nozzle, but the nozzle orifice would have to be large enough to accommodate the large capsules without clogging, and thus would not be able to generate inhalable particles.

-The capsules cannot be crushed or fractured with a high-speed homogenizer to yield a mixture of formulation and capsule fragments suitable for testing nor can they be easily dissolved.

-The formulation alone, without the capsular material, cannot be generated as an acceptable aerosol.

-The formulation within the capsules has a very low vapor pressure, therefore, will not pose an inhalation hazard if fractured on treated surfaces.

• The test material physically clogs the test animals' respiratory tract during inhalation exposure.

• The test material is a pesticidal paint product which coats the animals' fur, can't be removed by typical methods, has been demonstrated to be systemically toxic, and cannot be tested by nose only procedures.

• The test material is a large, non-friable granule which does not possess any volatile hazardous components. The performance of an attrition study is required to

demonstrate that the test material is non-friable. In addition to the above, if the granule is applied with water, it must be demonstrated that the integrity of the granule is maintained in the water phase and that ingredients are not released from granules into the water phase.

For additional guidance on acute inhalation waivers refer to the attached Agency memorandum, "Policy on Acute Inhalation toxicity Data Waivers."

Materials which do not meet any of the above criteria should undergo inhalation testing in accordance with Agency policy. Although the Agency is in the process of lowering the limit test concentration and relaxing the particle size requirements, waivers based solely on the inability of a material to be generated as an aerosol will still be necessary in some situations. The following outline includes procedures which should be employed prior to requesting an inhalation waiver based on inability to generate an acceptable test atmosphere:

1. Solid materials which are friable should be milled for at least 24 hrs and generated with the use of a particle size discriminating system (cyclone or baffling chamber).

2. Gums, waxes or resins (sticky or tacky materials) which do not meet the above criteria should be dissolved with an appropriate vehicle and generated with at least two nebulizing systems. If the toxicity of the vehicle is unknown, a vehicle control is required. If the material is conducive to desiccation and milling, this should also be tried.

3. Liquid materials of high viscosity should be diluted, if possible, with an appropriate vehicle and generated with at least two nebulizing systems. The highest test material concentration which yields an acceptable exposure atmosphere should be used when testing diluted materials. Further, if the toxicity of the vehicle is unknown, a vehicle control is required.

If the above methods and any other possible experimentation with the aerosol generation equipment do not permit the generation of an exposure aerosol with an MMAD below 4 microns, a complete and thorough description of all particle size reduction methods, aerosol generation techniques and the resulting particle size data should be included in the acute inhalation waiver request. Animals need not be exposed during these atmosphere generation trials.

NOTE: Vapor pressure levels are considered in relation to the toxicity of the material under consideration. A vapor pressure less than 10^{-4} mm Hg is considered "low" for materials which demonstrate moderate or low acute toxicity. When reporting vapor pressure data to the Agency, the levels for the complete formulation as well as each individual component should be included.

D. EYE IRRITATION

A waiver for the primary eye irritation study may be requested if any of the following conditions apply:

- The test material is corrosive to skin or has a pH less than 2 or greater than 11.5. Such products will be placed in eye irritation category I on the basis of potential eye effects.

- The test material has been placed in category I for primary dermal irritation. Such products will be placed in eye irritation category I on the basis of potential eye effects.

- The test material has been placed in category I for acute dermal toxicity.

- The product design prevents ocular exposure. Products such as tamper-proof roach traps and bait boxes often meet these criteria.

- Products composed of very large (unable to be retained in the eye), non-friable (as demonstrated by an attrition study*) granules or pellets may be appropriate for a waiver if the material retains its physical form under application conditions (i.e., it is not dispersed in water prior to application). Further, the size range of the granules which compose the product should be documented and submitted as part of the request.

E. DERMAL IRRITATION

A waiver for the primary dermal irritation study may be requested if any of the following conditions apply:

- The product design prevents dermal exposure. Products such as tamper-proof roach traps and bait boxes often meet these criteria.

- The test material is corrosive to skin or has a pH less than 2 or greater than 11.5. Such products will be placed in dermal irritation category I on the basis of potential dermal effects.

- The test material has been placed in category I for acute dermal toxicity. Such products will be placed in dermal irritation category I on the basis of potential dermal effects.

- The test material has been placed in category I for acute dermal toxicity.

• The test material is a pesticidal paint which will not allow dermal evaluation. In this situation the registrant should perform a preliminary exposure of the material to the test animal skin in order to determine the degree of adherence and/or dermal staining. All observations made during preliminary exposure as well as supporting acute toxicity data on the formulation components should be included in the waiver request.

• The test material contains strong dyes or pigments which will not allow dermal evaluation. In this situation the test material should be tested without the dye or pigment included in the test formulation.

F. DERMAL SENSITIZATION

A waiver for the dermal sensitization study may be requested if any of the following conditions apply:

• The product does not result in repeated dermal exposure under conditions of use. The possibility of repeated exposure is very high for pesticide products. Such waiver claims must be supported by ample information and address the likelihood of occupational use and repeated, yet infrequent, exposure over long periods of time.

• The test material is a pesticidal paint which will not allow dermal evaluation. In this situation the registrant should perform a preliminary exposure of the material to guinea pig skin in order to determine the degree of adherence and/or dermal staining. All observations made during preliminary exposure as well as supporting acute toxicity data on the formulation components should be included in the waiver request.

• The test material contains strong dyes or pigments which will not allow dermal evaluation. In this situation the test material should be tested without the dye or pigment included in the test formulation.

• The product is a biological pesticide as defined in Subdivision M of the Pesticide Testing Guidelines. The registrant, however, is required to report any incidents of hypersensitivity that occur. This must include a record of incidents of hyper-sensitivity for the subject product. If no incidents have occurred to date, the registrant must so state. Incidents occurring after the initial statement must be reported as adverse data under FIFRA Sec. 6(a)(2).

• The product design prevents dermal exposure. Products such as tamper-proof roach traps and bait boxes often meet these criteria.

• The product is corrosive to skin or has a pH less than 2 or greater than 11.5 at the

most dilute use concentration recommended on the product label.

NOTE: Dermal sensitization testing for plastic or woven fiber materials should be performed with the unaltered product since diluting the test material to achieve different concentrations may be impossible. Moistening these materials, however, is still required if it can be done. The dermal sensitization potential of the technical material may also be considered in these situations for labeling purposes.

G. SUPPLEMENTAL WAIVER INFORMATION

Insufficient Waiver Rationale

• Waiver requests based on precautionary labeling will not be accepted. For example, a claim that protective eyewear, respirator or protective clothing requirements are already on the product label does not justify an acute data waiver since pesticide users may not adhere to label precautions.

• Requests to "waive" data based on a lack of toxicity of the technical material will not be accepted. Since inert ingredients often play a significant role in pesticide toxicity, the acute toxicity of the technical material does not necessarily coincide with that of the end-use product. Under certain conditions mentioned above, however, the technical may be used to assist in determining the appropriate precautionary labeling. Such requests are not considered requests to waive data requirements since the requirement must still be met. These requests are simply a referral to another existing data base in order to satisfy the requirement.

• Waiver requests based on economic reasons, such as for products which do not generate sufficient profits to justify performing acute studies, will not be accepted. Appropriate labeling is required for all products regardless of economics.

*Standard Attrition Studies:

The Agency is currently in the process of determining the appropriate methods and parameters for a standardized attrition study to define a non-friable material. Until then, attrition studies should, to some degree, correlate with the "real world" situation encountered during shipping and subsequent handling of a material in regards to friability. In addition, the results obtained from the study should be easily related to a regulatory framework, i.e., the level of hazard resulting from fines produced during the attrition study must be determined.